Remarks

This paper is responsive to the Office Action mailed September 29, 2005, a response to which was due December 29, 2005. This paper is filed with a request for a 3 month extension of time.

Claims 24, 26, 27 31, 41, 42, 45-50, and 53-55 are pending in this application. Claims 24, 26, 27 31, 41, 42, 45-50, and 53-55 are rejected. By the present amendment, claims 24, 26, 31, 41, 42, 45-49, and 53-55 are hereby amended, claim 50 is hereby canceled, and new claim 56 is added. The amendments and new claim, which recite a vaccine for protecting an animal subject against *B. anthracis*, are fully supported by application as filed, and thus add no new matter.

Priority

Applicant's claim for domestic priority under 35 U.S.C. § 119(e) was acknowledged. However, the Office stated that the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. § 112 for claims 24, 26, 27, 31, 41, 42, 45-50 and 53-55 of this application. The Office states that the provisional application does not provide any written description or contemplate LF mutant proteins or fragments thereof that lack metalloproteinase activity. Therefore, the Office asserts that this application is entitled only to the instant filing date for prior art purposes.

Applicant respectfully points out that on page 4 starting at the second line from the bottom of provisional document 60/171,459, a mutant form of LF containing the portion of the LF gene which encodes amino acids 50 to 250, which corresponds to amino acids 83 to 283 of SEQ ID NO:2 as listed in the instant application, is described. It is clear that the provisional application describes and contemplates LF mutants, as the LF described is not wild-type, but rather deletion mutants, i.e., LF fragments. Furthermore, according to S.E. Hammond and P.C. Hanna, "Lethal Factor Active-Site Mutations Affect Catalytic Activity In Vitro", Infection and Immunity, May 1998, Vol. 66, No. 5, p. 2374-2378 (courtesy copy enclosed and in a supplemental IDS that will be filed under separate cover) the carboxy terminus of LF, amino acids 449 to 809 of SEQ ID NO:2 as listed in the instant application, contains the catalytic metalloproteinase domain. It was well established in the art prior to the filing date of the provisional application that an amino terminal fragment of LF, for example the portion of the LF

gene which encodes amino acids 83 to 283 of SEQ ID NO:2 as listed in the utility application, would clearly lack metalloproteinase activity as it contains no portion of the metalloproteinase domain. Therefore, Applicant respectfully requests that the claim for domestic priority under 35 USC § 119(e) be allowed.

Furthermore, pursuant to 37 C.F.R. § 1.57 Applicant notes that a portion of Provisional application 60/171,459 was inadvertently omitted from the specification and the priority claim is to be considered an incorporation by reference of the inadvertently omitted portion of the specification. Applicant has amended the instant application to include the inadvertently omitted portion, is supplying a copy of the provisional application, and wishes to identify that the inadvertently omitted portions can be found starting on page 4 line 13 running through page 6 line 18, as well as Table 1 on page 9 and Figure 1 on page 10 of the provisional application. Applicant has changed the text of the omitted portions only to provide clarity as to SEQ ID NOs, Table and Figure numbering.

Claim Objections

Claims 46 and 48 are objected to under 37 C.F.R. § 1.75(c) as being of improper independent form for failing to further limit the subject matter of a previous claim. Applicant has amended the claims to satisfy the objections.

Claim Rejections - 35 U.S.C. § 112

Claims 24, 26, 27, 31, 41, 42, 45-50, and 53-55 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims allegedly contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Office asserts that claims directed to the genus of LF mutants and fragments thereof are unpatentable due to a lack of written description for the broad class. Applicant respectfully notes that, at the time the instant application was filed, a number of LF mutants that lack metalloproteinase activity were known in the art. These include the mutants of LF as shown in Klimpel et al. (1994) (previously disclosed by Applicant in an IDS), H686A (corresponding to H719 of SEQ ID NO:2), H690A (corresponding to H723 of SEQ ID NO:2), H686A/H690A double mutant, as well as the E687C mutant explicitly described in the instant application

(corresponding to E720 of SEQ ID NO:2). Furthermore, Hammond and Hanna (1998) disclose an E687D mutant and also teach that all the mutants of Klimpel et al. (1994) as well as the E687D mutant are stable full length molecules that lack metalloproteinase activity. It is clear that the art does teach a genus of mutant LFs that lack metalloproteinase activity. One of ordinary skill in the art could readily ascertain the nucleotide sequence of the above mentioned LF mutants. Also, one of ordinary skill in the art could without any undue experimentation make further mutants of LF and assay them for metalloproteinase activity. The instant application and the prior art unambiguously convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

Applicant further respectfully notes that Arora and Leppla (1993) (previously disclosed by Applicant in an IDS) disclose LF deletion mutants, i.e., fragments of LF that lack metalloproteinase activity, for example amino acids 1 to 254 (corresponding to amino acids 34 to 287 of SEQ ID NO:2), amino acids 1 to 198 (corresponding to amino acids 34-231 of SEQ ID NO:2), and amino acids 1 to 79 (corresponding to amino acids 34 to 112 of SEQ ID NO:2). Since none of these fragments contain the C-terminal metalloproteinase domain, one of ordinary skill in the art can clearly appreciate that the fragments lack metalloproteinase domains. It is also clear that the art does teach a genus of LF fragments that lack metalloproteinase activity. One of ordinary skill in the art could readily ascertain the nucleotide sequence of the above mentioned LF fragments. Also, one of ordinary skill in the art could without any undue experimentation make further fragments of LF and assay them for metalloproteinase activity. The instant application and the prior art unambiguously convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

Applicant would like to point out that a revised supplemental amendment was filed on November 7, 2003, to clarify that the cysteine residue at position 687 of the amino acid sequence shown in Figure 1B, corresponds to amino acid 720 of SEQ ID NO:2. This should clarify for the Office that the replacement of the glutamic acid residue at position 720 of SEQ ID NO:2 with a cysteine corresponds to the mutation of the glutamic acid residue at position 687 with a cysteine in the Klimpel et al. (1994) reference, not the glutamic acid residue at position 720 of the same reference which corresponds to amino acid 753 of SEQ ID NO:2. Applicant respectfully notes that there was no mixing and matching of different concepts as claimed by the Office, nor did

Applicant ever claim a mutant which has metalloproteinase activity.

The Office also claims that the art does not teach a genus of naturally occurring PA proteins. Applicant directs the Office to Price et al. "Genetic Diversity in the Protective Antigen Gene of *Bacillus anthracis*", Journal of Bacteriology, April 1999, Vol. 181, No. 8, p. 2358-2362 (courtesy copy enclosed and a supplemental IDS listing this article will be filed under separate cover). Price et al. sequenced the PA gene from 26 *B. anthracis* strains and teach 8 different genotypes and 4 phenotypes of PA (see Table 4). Clearly the art teaches a genus of naturally occurring mutants of PA. One of ordinary skill in the art could readily ascertain the nucleotide sequence of the above mentioned PA mutants. Also, one of ordinary skill in the art could identify other naturally occurring mutants of PA by simply sequencing the PA gene of more *B. anthracis* strains, and assay the PA mutants for activity. The instant application and the prior art unambiguously convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

Applicant further wishes to point to Brossier et al. "Functional Analysis of the Carboxy-Terminal Domain of *Bacillus anthracis* Protective Antigen", Infection and Immunity, Feb. 1999, Vol. 67, No. 2, p 964-967 (courtesy copy enclosed and in a supplemental IDS that will be filed under separate cover) for support of PA mutants where amino acids 711 to 721, corresponding to amino acids 740 to 750 of SEQ ID NO:4, and amino acids 705 to 722, corresponding to amino acids 734 to 751 of SEQ ID NO:4, were deleted (see Figure 1) without hindering the activity of PA. One of ordinary skill in the art could readily ascertain the nucleotide sequence of the above mentioned PA mutants. Also, one of ordinary skill in the art could identify other mutants of PA and assay the PA mutants for activity. The instant application and the prior art unambiguously convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

Applicant wishes to even further point to Varughese et al. "Identification of a Receptor-Binding Region within Domain 4 of the Protective Antigen Component of Anthrax Toxin", Infection and Immunity, April 1999, Vol. 67, No. 4, p. 1860-1865, for support of even more PA mutants that function without hindrance (see Figure 2). One of ordinary skill in the art could readily ascertain the nucleotide sequence of the above referenced PA mutants. Also, one of ordinary skill in the art could identify other mutants of PA and assay the PA mutants for activity.

The instant application and the prior art unambiguously convey to one skilled in the relevant art that Applicant, at the time the application was filed, had possession of the claimed invention.

Applicant believes that the instant application and the state of the art at the time of filing more than sufficiently satisfy the written description requirement for the claimed LF and PA polynucleotides, and respectfully requests withdrawal of the rejection.

Specifically as to claim 50, Applicant cancels the claim.

Claim Rejections - 35 U.S.C. § 103

Applicant acknowledges the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Office to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a). The subject matter of the various claims was commonly owned at the time any inventions covered therein were made.

Claims 24, 26, 31, 42, 46, 48, 49, 53 and 54 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Gu et al. (Vaccine, 1(4):340-344, Feb. 1999, publicly available online January 4, 1999) in view of Brossier et al. (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al. (Infection and Immunity, 52(2):509-512, 1986), Singh et al. (Infection and Immunity 66(7):3447-48, July 1998), Park et al. (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al. (Annu. Rev. Immunol. 15:617-48, 1997).

The Office contends that "it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the immunogenic DNA vaccine comprising PA of Gu et al with a DNA vaccine according to Donnelly et al comprising the detoxified LF of Brossier et al and optionally an additional DNA vaccine made according to Donnelly et al comprising the comprising the detoxified EF of Brossier et al because Little et al and Singh et al teach that LF and EF may also play an important role in providing immunity, Brossier et al teach that a live vaccine vector strain of *B. anthrasis* comprising PA along with the detoxified LF and EF produced a strong antibody response and Park et al teach that the understanding of action of toxin predicts that immunization with inactive LF or EF would augment protection and that inclusion of the inactive LF along with PA may provide for a safer vaccine. Vaccine production includes a promoter/enhancer for high levels of gene expression in mammalian cells". (See page 13 of the Office Action.)

Applicant respectfully submits that the priority claim to provisional document 60/171,459, with a filing date of December 22, 1999, is proper and therefore the Brossier et al. (2000) and Park et al (2000) references are not prior art and cannot be used under 35 U.S.C. § 103(a). The remaining references, namely Gu et al., Little et al., Singh et al., and Donnelly et al. do not teach or suggest a vaccine that protects against *B. anthracis* and that comprises i) a first polynucleotide which a) encodes an LF protein or LF fragment that lacks metalloproteinase activity and contains amino acids 83 to 283 of SEQ ID NO:2, and b) is operably linked to a promoter which drives expression of said LF protein or fragment thereof in cells of a mammalian subject, and ii) a second isolated polynucleotide which encodes a *B. anthracis* protective antigen (PA) protein, or a fragment thereof that a) contains amino acids 204 to 764 of SEQ ID NO:4, and b) is operably linked to a promoter which drives expression of said PA protein or fragment thereof in cells of a mammalian subject, as recited in claims 24, 54, and 55, as amended. Accordingly, Gu et al. Little et al, and Donnelly et al. do not render amended claims 23, 54, and 55, or the claims that depend therefrom obvious. Applicant respectfully requests withdrawal of the rejection.

Clams 27, 41, 45, 47, 53 and 55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gu et al. (Vaccine, 1(4):340-344, Feb. 1999, publicly available online January 4, 1999) in view of Brossier et al. (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al. (Infection and Immunity, 52(2):509-512, 1986), Singh et al. (Infection and Immunity 66(7):3447-48, July 1998), Park et al. (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al. (Annu. Rev. Immunol. 15:617-48, 1997) as applied to claims 24, 26, 31, 42, 46, 48, 49, 53 and 54 above, further in view of Glorioso et al. (USPN 5,998,174).

It is the Office's contention that "it would have been *prima facie* obvious to one of ordinary skill in the art to modify the DNA vaccine as combined supra by cloning the nucleic acid encoding the PA, detoxified LF and optionally the detoxified EF into the multigene HSF viral vector of Glorioso et al because Glorioso et al teach that multiple bacterial immunogens can be produced from a single viral vector an that the multigene HSV vector can also be applied as a vaccine". (See page 14 of the Office Action.)

Glorioso et al. do not provide the teachings or suggestions absent from Gu et al., Little et al., Singh et al., and Donnelly et al. Accordingly, Glorioso et al al, alone or combination with Gu et al., Little et al, Singh et al. and Donnelly et al. do not render claims 24 and 54, or any of

the claims that depend therefrom, including claims 26, 31, 42, 46, 48, 49, and 53 obvious. Applicant respectfully requests withdrawal of the rejection.

Claim 53 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Gu et al. (Vaccine, 1(4):340-344, Feb. 1999, publicly available online January 4, 1999) in view of Brossier et al. (Infection and Immunity, 68(4):1781-1786, April 2000), Little et al. (Infection and Immunity, 52(2):509-512, 1986), Singh et al. (Infection and Immunity 66(7):3447-48, July 1998), Park et al. (Protein Expression and Purification, 18:293-302, April 2000) and Donnelly et al. (Annu. Rev. Immunol. 15:617-48, 1997) as applied to claims 24, 26, 31, 42, 46, 48, 49, 53 and 54 above, further in view of Felgner et al. (USPN 6,710,035).

The Office states that "it would have been *prima facie* obvious to one having ordinary skill in the art to substitute mRNA nucleic acids for the DNA plasmids in the composition as combined supra because Felgner et al teach that mRNA can be used to express immunogenic polypeptides in muscle and other non-replicating tissue". (See page 15 of the Office Action.)

Felgner et al. do not provide the teachings or suggestions absent from Gu et al., Little et al, Singh et al. and Donnelly et al. Accordingly, Glorioso et al al, alone or combination with Gu et al., Little et al, Singh et al. and Donnelly et al. do not render claim 24, or any of the claims that depend therefrom, including claim 53 obvious. Applicant respectfully requests withdrawal of the rejection.

Citation of Relevant Art

Applicant notes that the following prior art has been made of record as cumulative to the secondary references above to establish conventional means of delivery of nucleic acid expression vectors to cells for heterologous protein expression: Powell et al. (U.S. Patent 5,877,159), Ramshaw et al. (U.S. Patent 5,866,136); and Palese et al. (U.S. Patent 5,854,037).

If there is any fee due in connection with the filing of this Response, please charge the fee to our Deposit Account No. 03-0172.

Respectfully submitted,

Date: March 29, 2006

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